PSJ17 Exh 98

Template Letter of Medical Necessity [BTP, Chronic Low Back Pain, 02-2008]

{Date}

{Medical Director's Name
Medical Director
Insurer Name
Address
City, State Zip}

Re: Denied Prescription Drug Claim for FENTORA®(fentanyl buccal tablet) [C-II] Therapy

Dear ***{Name or contact}***:

Although FENTORA is not FDA-approved for the management of breakthrough pain (BTP) in patients with chronic noncancer pain conditions, I would like to appeal this denial and provide information to support the medical necessity of using FENTORA for enrollee ***{patient name and policy number}***.

I am writing regarding a recently denied prior authorization request for FENTORA by ***{health plan name}*** for this patient due to ***{his/her}*** diagnosis of chronic low back pain. FENTORA is indicated only for the management of BTP in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.[1]

With this letter, I will provide information concerning ***{patient name}***'s medical history, diagnosis and treatment(s), as well as available clinical data about the use of FENTORA in this patient population. I will describe my rationale for choosing FENTORA therapy for this patient.

Patient Information

{Healthcare Professional should populate with information regarding the patient's medical history, diagnosis, treatment(s)}

Use of Opioids in Chronic Pain

Dosing guidelines for opioid therapy for the management of chronic pain are based on extensive clinical experience in various medical conditions. Several guidelines that support the judicious use of opioids for the management of chronic pain have been published by key medical organizations, including the American Pain Society, the American Academy of Pain Medicine, the American Society of Anesthesiologists, the Federation of State Medical Boards of the United States, and the American College of Physicians.[2,3,4,5,6,7,8,9]

Template Letter of Medical Necessity [BTP, Chronic Low Back Pain, 02-2008]

Clinical Data

12-week Randomized, Double-blind, Placebo-controlled Study

A 12-week multicenter, open-label study with 3 within-patient, randomized, double-blind placebo-controlled treatment periods was conducted to evaluate the efficacy and safety of FENTORA in opioid-tolerant patients with BTP associated with chronic noncancer pain conditions, including low back pain.[10] This was the first study to evaluate the efficacy and safety of BTP treatment over a 3-month period.

Eligible opioid tolerant adult patients experienced, on average, 1-4 BTP episodes per day which were partially controlled with rescue opioid medications. The study included an initial open-label titration phase followed by a 12-week, open-label treatment period with 3 within-patient, double-blind placebo-controlled treatment phases occurring after 4, 8, and 12 weeks of treatment. Patients entered the initial open-label dose titration phase to identify a successful dose of FENTORA defined as the single dose of 100-800 mcg providing adequate pain relief for at least 2 of 3 BTP episodes without unacceptable adverse events (AEs). Patients who entered the 4-week open-label treatment period received FENTORA at their effective dose followed by a double-blind, randomized treatment for 9 consecutive BTP episodes (6 episodes were treated with FENTORA and 3 with placebo). At the completion of this phase, patients began the second open-label treatment period. The open-label/ double-blind sequence was repeated twice.

During the double-blind evaluation periods (occurring after 4, 8 and 12 weeks of treatment), pain intensity (PI, 11-point numeric scale, 0=none to 10=worst possible pain) and pain relief (PR, 5-point numeric scale, 0=no relief to 4=complete relief) scores were assessed at each time point (5, 10, 15, 30, 45, 60, 90, and 120 minutes) following treatment. The primary efficacy measure was the sum of pain intensity differences from 5 minutes though 60 minutes ($SPID_{60}$) after administration of study drug following week 12 (double-blind treatment 3). Secondary outcome measures included PID and PR at each time point during the double-blind periods (following 4, 8 and 12 weeks of treatment).

In this study, the responses to FENTORA were consistent across clinically meaningful measures after 12 weeks of treatment. The study met the primary endpoint. Improvement in pain intensity was observed as early as 15 minutes and pain relief was observed as early as 5 minutes following treatment with FENTORA compared with placebo. Adverse events were generally typical of opioids.

Randomized, Double-blind, Placebo-Controlled Study with Chronic Low Back Pain

A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy and tolerability of FENTORA compared to placebo in alleviating breakthrough pain in patients with underlying chronic low back pain (associated with degenerative disc disease, osteoarthritis, spondylolisthesis) and who were tolerant to opioid therapy.[11] These patients were on stable doses of around-the-clock (ATC) opioid medications (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 mcg/hr, oxycodone ≥30 mg/day, oral hydromorphone ≥8 mg/day or an equianalgesic dose of another opioid) for 7 days or longer prior to study enrollment for their persistent pain.

Template Letter of Medical Necessity [BTP, Chronic Low Back Pain, 02-2008]

The initial open-label dose-titration phase identified an effective dose of FENTORA (defined as the dose strength that provided satisfactory relief of BTP within 30 minutes for ≥2/3 episodes without unacceptable AEs). During the dose titration period, patients discontinued the study if they did not obtain satisfactory relief from BTP at any dose including the maximum dose of 800 mcg of FENTORA or if they experienced intolerable AEs. The patients who entered the double-blind phase were randomized to 1 of 3 sequences in which 9 BTP episodes were treated (6 episodes with FENTORA and 3 with placebo).

Pain intensity (PI) and pain relief (PR) scores were assessed at each time point (5, 10, 15, 30, 45, 60, 90, and 120 minutes) following treatment. Pain intensity differences (PID) between each time point and pre-treatment pain were calculated. The sum of pain intensity differences for the first 60 minutes from baseline ($SPID_{60}$) was the primary efficacy measure. Secondary outcome measures included PID and PR at each time point, the proportion of treated BTP episodes with ≥33% and ≥50% reduction in PI score, patient assessment of time to meaningful PR, and use of usual BTP medication.

Key findings from this study showed the following:

Patient Demographics/Baseline Characteristic

- The mean age of the patients in this study was 48 years, the majority were Caucasian (89%) and 54% were female.
- The most common primary etiology of chronic low back pain included degenerative disc disease (70%), osteoarthritis (7%), spondylolisthesis (5%), or other eligible low back pain etiologies (18%; most common "other" low back pain etiologies included myofascial pain, herniated disk, spondyloarthopathy)
- At baseline, the most common (≥10%) ATC opioid medications used at baseline were oxycodone (36%), transdermal fentanyl (26%), morphine (17%), methadone (12%), and hydrocodone-acetaminophen (12%). The median oral morphine equivalent taken as ATC dose for patients on transdermal fentanyl was 150 mg/day (range 60 to 360 mg) and for those patients taking other ATC opioid medications was 160 mg (range 45 to 17500 mg).
- At baseline, the most common (≥10%) rescue medications used were hydrocodone/ hydrocodone combination products (38%), oxycodone (22%), oxycodone combination products (17%), and fentanyl/fentanyl citrate (14%). The median oral morphine equivalent taken as rescue medication for BTP was 20 mg/BTP episode (range 5 to 120 mg).

Patient Disposition

- A total of 81% (84/104) of patients achieved an effective dose of FENTORA between 100-800 mcg during the open-label dose titration phase (105 patients entered this period, 104 received at least 1 dose of FENTORA and were evaluable for safety, 77 completed this phase, and 27 (26%) patients discontinued from the study of which 11 patients withdrew due to intolerable AEs).

  - No simple linear relationship was found between the effective dose of FENTORA and the dose of the ATC opioid taken during the study or the average dose of rescue medication used prior to the study.
- 77 patients entered the double-blind treatment period, 75 completed this phase; 2 (2%) patients withdrew from this phase due to AE (1 patient) and consent withdrawal and 73 were efficacy evaluable.

Efficacy

- The primary efficacy measure, $SPID_{60}$, was significantly higher for FENTORA than placebo (8.3 vs. 3.6, respectively, $p<0.0001$).
- Significant differences in PID scores following FENTORA compared with placebo started at 10 minutes ($p<0.02$) and for all subsequent time points ($p<0.0001$) up to 120 minutes.
- Mean PR scores were significantly higher following treatment with FENTORA than with placebo as early as 15 minutes ($p=0.0002$) and at all subsequent time points ($p<0.0001$) up to 120 minutes.
- Clinically significant (≥33%) decreases in PI scores from baseline were significantly greater for FENTORA (20% of episodes) versus placebo (11% of episodes) at 15 minutes ($p<0.01$) and at all subsequent time points ($p<0.0001$). It is generally recognized that a 33% or greater reduction in pain intensity is a clinically significant improvement and is best associated with not needing an additional dose of rescue medication.[12,13,14]
- A ≥50% improvement in PI from baseline was observed with FENTORA versus placebo at 30 minutes (30% vs. 13% of episodes, respectively, $p=0.0001$) and at all subsequent time points through 120 minutes ($P<0.0001$).
- Patients experienced meaningful PR for more BTP episodes treated with FENTORA than placebo (70% vs. 30%, respectively, $p<0.0001$). Meaningful PR was achieved by 30 minutes in 38% of BTP episodes treated with FENTORA vs. 16% for placebo.
- Patients receiving placebo were to use supplemental opioids for BTP episodes compared to those receiving FENTORA (risk ratio, 95% confidence interval (CI)).
- Rescue medication was used for 96 (46%) of 207 BTP episodes for which placebo was used compared to 65 (16%) of 413 BTP episodes for those receiving FENTORA. These data resulted in a relative risk ratio of 0.22, with 95% confidence interval (CI) 0.13-0.35. Therefore, patients receiving placebo were more than 4 times as likely to use supplemental opioids for BTP episodes as those receiving FENTORA.

Safety Profile

- In this study, FENTORA was generally well tolerated in the dose range of 100 mcg to 800 mcg. Overall, AEs were reported by 65% of patients.
- The most frequently (≥10%) occurring AEs were nausea (19%), and dizziness (13%), which are typical of opioid side effects. Incidence of AEs was higher during the dose-titration period (57%) than during the double-blind phase (34%).
- Mild and transient application site AEs (irritation, discoloration, erythema, and ulcer) were reported in 6 patients (5 in dose-titration phase and 1 in the double-blind period), of which only one patient discontinued the study at the end of the dose-titration phase.

- Twelve patients discontinued the study due to AEs. A total of 11 patients withdrew from the study during the dose-titration phase.
- Serious adverse events were reported in two patients (accidental overdose resulting in loss of consciousness was considered to be possibly related to the study drug by the investigator [patient recovered after administration of oxygen] and diabetic gastroparesis was considered to be unrelated).

In summary, in the clinical trial of FENTORA for chronic low back pain, approximately 80% of patients found an effective dose of FENTORA in the range of 100 mcg to 800 mcg. FENTORA was found to be efficacious compared to placebo, producing treatment differences as early as 10 minutes after start of FENTORA administration, increasing through 60 minutes and maintained through 120 minutes, the last time point measured. Pain relief was significantly greater with FENTORA than with placebo occurring as early as 15 minutes and at all subsequent time points through 120 minutes following treatment with FENTORA. Most of the AEs observed were typical of opioid side effects. One reported serious adverse event was considered by the investigator to be possibly related to the study drug (accidental overdose with unresponsiveness to pain stimuli).

Open-label Study

An 18-month, open-label study was conducted to evaluate the long-term safety and tolerability of FENTORA in opioid-tolerant patients with BTP and chronic noncancer pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, complex regional pain syndrome, chronic low back pain, traumatic injury, osteoarthritis or chronic headache.

Eligible patients experienced 1-4 BTP episodes per day and were managed with ATC opioid medications (oral morphine ≥60 mg/day, or an equianalgesic dose of another opioid as ATC therapy, or transdermal fentanyl ≥50 mcg/hr, for 7 days or longer prior to enrollment into the study) for their persistent pain. This study was open to new patients (those naïve to FENTORA) and to patients who had completed 1 of 2 randomized double-blind FENTORA efficacy studies. For new patients, the study consisted of a screening visit, a dose-titration period and an 18-month open-label maintenance period. The effective dose for treatment naïve patients (100-800 mcg) was determined during the dose-titration period and was defined as the single dose strength of FENTORA that provided adequate analgesia (sufficient pain relief within 30 minutes), for each of approximately 2 of 3 BTP episodes, without unacceptable AEs for the majority of BTP episodes. For patients who had previously participated in either of the two short-term double-blind studies discussed above, the study consisted of only an 18-month maintenance treatment period at their previously identified effective dose.

In this long-term safety study, interim safety data was published for 94 patients.[15] In addition, interim analysis for 632 enrolled patients have been presented that evaluated the impact of FENTORA on mood, functioning and quality of life,[16] and also evaluated the overall performance and patient preference of FENTORA relative to that of the patients' previous BTP therapy.[17] The most common primary painful condition included chronic low back pain (59%), traumatic injury (10%), osteoarthritis (6%), chronic headache (5%), complex regional pain syndrome (4%) or diabetic peripheral neuropathy (3%).

Preliminary results from this study demonstrated the following:

Safety Profile

Interim safety data was published for 94 patients.[15] FENTORA was generally well tolerated in the dose range of 100 mcg to 800 mcg with a relatively low incidence of AEs (23%).

- The most common AEs that occurred in the 94 patients were nausea (7%), dizziness (5%), back pain (4%), headache (4%), dyspepsia (3%), application site pain (2%), arthralgia (2%), and anxiety (2%).
- Four patients reported oral mucosal AEs (pain, irritation, ulceration, or vesicles) associated with tablet application site which resolved within 1-15 days for 3 patients. The resolution time for the fourth patient was unknown.
- There were no reports of respiratory depression or death.

Mood, Functioning and Quality of Life

- Preliminary analysis at Month 9 involving 189 evaluable patients demonstrated that patients treated with FENTORA showed trends toward improvements from baseline to 9 months in the majority of mood, functioning and quality of life measurements, based on changes in the 36-item Short-Form Health Survey (SF-36) and Profile of Mood States (POMS).[16]
- Patients with moderate or severe pain at baseline experienced greater improvements in mood and quality of life following treatment with FENTORA than those with mild pain.[16]

Patient Preference Assessment

- Global Medication Performance (GMP) was assessed at Month 9 involving 189 evaluable patients. The majority of patients (93%) rated the global medication performance of FENTORA to be "good", "very good" or "excellent" for the management of their BTP.[17]
- The Medication Preference questionnaire that was completed at month 1 was assessed in 477 evaluable patients. The majority of patients (89%) preferred FENTORA to their previously used rescue medication at 1 month. Most patients reported that FENTORA provided a faster onset of relief than their previous rescue medication (94%), was easier to administer (70%), and was more convenient to use (69%) than their previous medications used for rescue at 1 month.[17]

In summary for this study, FENTORA was well tolerated at doses ranging from 100 to 800 mcg for the management of BTP in opioid-tolerant patients with noncancer chronic pain. Based on the results of this analysis, the majority of patients in this study preferred FENTORA compared to their previously used rescue medication.

FENTORA Product Summary[1]

FENTORA is indicated only for the management of breakthrough pain (BTP) in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for

their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

In a pivotal trial of FENTORA, onset of efficacy was demonstrated within 15 minutes in some opioid tolerant cancer patients, with duration of efficacy demonstrated up to 60 minutes (last time point measured).

Important Safety Information

- Postmarketing reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. These deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing.
- Use FENTORA only for labeled indications
- FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.
- FENTORA is contraindicated in the management of acute pain, postoperative pain, headache or migraine.
- FENTORA is not a generic version of Actiq (oral transmucosal fentanyl citrate). When prescribing, do not convert patients from Actiq to FENTORA on a mcg per mcg basis. When dispensing, do not substitute FENTORA for other fentanyl products as this may result in fatal overdose.
- Follow dosing instructions carefully:
  - For opioid tolerant patients not being converted from Actiq, the initial dose of FENTORA is always 100 mg.
  - For patients being converted from Actiq, please consult the Initial Dosing Recommendations table in the enclosed prescribing information for FENTORA.
  - Patients should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.
  - Patients should NOT take more than 2 doses of FENTORA per BTP episode (separated by at least 30 minutes using the same dosage strength)
  - Patients MUST wait at least 4 hours before treating another BTP episode with FENTORA

Template Letter of Medical Necessity [BTP, Chronic Low Back Pain, 02-2008]

- FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.

- Patients and caregivers must be instructed that FENTORA contains a medicine in an amount that can be fatal to a child and thus, should keep all tablets out of the reach of children, and properly discard of any unused tablets as soon as they are no longer needed.

- Use with strong or moderate cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

In FENTORA cancer clinical trials, FENTORA was generally well tolerated at doses of 100 mcg to 800 mcg. The most frequently occurring adverse events (≥10% of patients in either titration or post-titration) were nausea, vomiting, fatigue, dizziness, anemia, constipation, peripheral edema, dehydration, asthenia and headache. No corrections were made for concomitant use of around-the-clock opioids or cancer-related symptoms. In addition, application site reactions, which occurred in 10% of patients in all FENTORA studies, tended to occur early in treatment, were self-limited, and resulted in treatment discontinuation in 2% of patients.

Rationale for Therapy

{Healthcare Professional should populate with his/her own clinical judgment for use of this therapy in his/her patient.}

Thank you for your consideration. Please contact me at ***{physician telephone number}*** if you require additional information.

Sincerely,
{Physician Name
Title}

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[1] FENTORA® (fentanyl buccal tablet) [Current approved prescribing information]. Frazer, PA: Cephalon, Inc.

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[3] AAPM/APS. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society. Glenview, IL:American Academy of Pain Medicine and American Pain Society, 1996. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed 18 October 2007.

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[16] Nalamachu S, Xie F, Messina J, et al. Mood, functioning, and quality of life in opioid-tolerant patients with noncancer chronic pain and breakthrough pain: Effect of fentanyl buccal tablet (FBT). [Poster presentation]. Presented at the 26th Annual Scientific Meeting of the American Pain Society. Washington, DC, May 2-5, 2007.

[17] Nalamachu S, Xie F, Messina J, et al. Patient preference for fentanyl buccal tablet (FBT) in the management of breakthrough pain: Open-label evaluation in opioid-tolerant patients with chronic noncancer pain. [Poster presentation]. Presented at the 26th Annual Scientific Meeting of the American Pain Society. Washington, DC, May 2-5, 2007